(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 3 722 258 A1**

(12) **EUROPEAN PATENT APPLICATION**
published in accordance with Art. 153(4) EPC

(43) Date of publication:
14.10.2020 Bulletin 2020/42

(21) Application number: **18885442.6**

(22) Date of filing: **07.12.2018**

(51) Int Cl.:
C01B 7/00 *(2006.01)* ***G21G 4/08*** *(2006.01)*

(86) International application number:
PCT/JP2018/045068

(87) International publication number:
WO 2019/112034 (13.06.2019 Gazette 2019/24)

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR
Designated Extension States:
BA ME
Designated Validation States:
KH MA MD TN

(30) Priority: **07.12.2017 JP 2017235141**

(71) Applicant: **Osaka University**
Suita-shi, Osaka 565-0871 (JP)

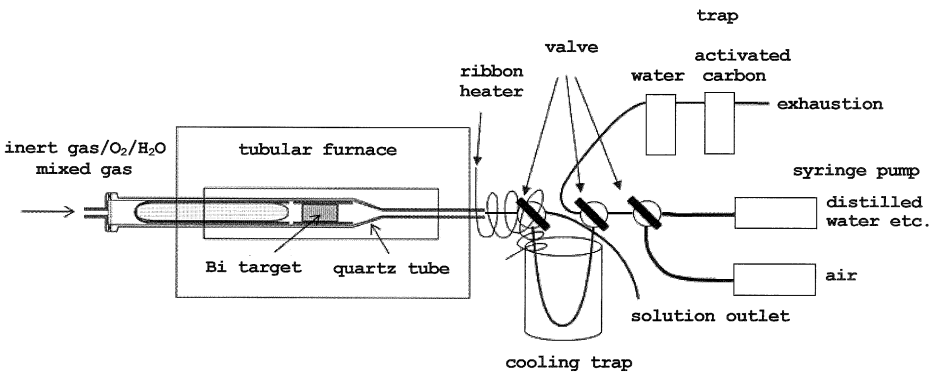
(72) Inventors:
- **SHINOHARA, Atsushi**
  Suita-shi
  Osaka 565-0871 (JP)
- **TOYOSHIMA, Atsushi**
  Suita-shi
  Osaka 565-0871 (JP)
- **YOSHIMURA, Takashi**
  Suita-shi
  Osaka 565-0871 (JP)
- **KANDA, Akimitsu**
  Suita-shi
  Osaka 565-0871 (JP)

(74) Representative: **J A Kemp LLP**
14 South Square
Gray's Inn
London WC1R 5JJ (GB)

(54) METHOD FOR PRODUCING ASTATINE

(57) Provided is a method capable of separating and purifying astatine-211 in a high yield and dissolving same in a solution. A method for producing astatine-211, including a step of irradiating α ray to bismuth to produce astatine-211 in the bismuth, and a step of distilling the bismuth that received α ray irradiation with a carrier gas containing an inert gas, O_2 and H_2O to separate and purify astatine-211, and dissolving the astatine-211 in a solution.

Fig. 1



EP 3 722 258 A1

Description

[Technical Field]

[0001] The present invention relates to a production method of astatine.

[Background Art]

[0002] Utilization of Astatine-211 (At-211), which is an α ray emitting nuclide, for an α ray internal therapy has been expected since the 1950s, and the research for its clinical application has been actively performed in recent years. For application of astatine to clinical research, it is necessary to first generate astatine by irradiating a metallic bismuth target with an α beam using an accelerator, separate and purify astatine from the metal bismuth, and prepare an astatine solution for labeled drug synthesis to be performed next. Dry methods and wet methods are used as astatine separation and purification methods. In the wet method, since bismuth metal containing astatine is dissolved and then extracted by solvent extraction, it has the disadvantage of being contaminated by impurities derived from the reagent. On the other hand, in the dry method, metal bismuth containing astatine is heated to separate astatine by distillation, and then astatine is transported by airflow to allow for cooling trap, and dissolved in a solution. Thus, contamination of impurity is extremely low. However, in the conventional dry method, it is necessary to add an oxidant (non-patent document 1) and sodium hydroxide (non-patent document 2) to increase the recovery rate of astatine, and chemical constraints are imposed on the synthesis conditions of the astatine-labeled drug in the next step. Therefore, a new method permitting free selection of the solution properties and affording a high concentration astatine solution stably in a high yield is demanded.

[Document List]

[non-patent documents]

[0003]

non-patent document 1: E. Aneheim et al., Scientific Reports, 5, 12025 (2015).
non-patent document 2: K. Nagatsu et al., Applied Radiation and Isotopes, 94, 363-371 (2014).

[Summary of Invention]

[Technical Problem]

[0004] The purpose of the present invention is to provide a method capable of preparing astatine-211 in a high yield as a solution for labeled drug synthesis.

[Solution to Problem]

[0005] The present inventors have conducted intensive studies in an attempt to solve the aforementioned problem and found that astatine-211 can be separated and purified in a high yield and easily dissolved in a solution by distillation of a metallic bismuth target irradiated with an α beam with a carrier gas containing an inert gas, O_2 and H_2O, which resulted in the completion of the present invention.

[0006] That is, the present invention provides the following.

[1] A method for producing astatine-211, comprising a step of irradiating α ray to a metallic bismuth target to produce astatine-211 in the bismuth target, and a step of distilling the bismuth target that received α ray irradiation with a carrier gas comprising an inert gas, O_2 and H_2O to separate and purify astatine-211, and dissolving the astatine-211 in a solution.
[2] The method of [1], wherein the inert gas is He or N_2.
[3] The method of [1] or [2], wherein the volume ratio of the inert gas:O_2 in the carrier gas is 99:1 to 51:49 and the content of H_2O is 1 to 15 $\mu g/cm^3$.
[4] The method of any one of [1] to [3], wherein the flow rate of the carrier gas is 5 to 40 mL/min.
[5] The method of any one of [1] to [4], wherein the distillation temperature is 500 to 850°C.

[Advantageous Effects of Invention]

[0007] According to the present invention, a method capable of separating and purifying astatine-211 in a high yield and dissolving same in a solution is provided.

[Brief Description of Drawings]

[0008] Fig. 1 is a schematic drawing showing one embodiment of an apparatus for carrying out step 2 of the method of the present invention.

[Description of Embodiments]

[0009] The present invention is explained in detail below.

[0010] The production method of astatine-211 of the present invention includes
a step of irradiating α beam to a metallic bismuth target to produce astatine-211 in the bismuth target (hereinafter to be referred to as step 1), and
a step of distilling the bismuth target that received α ray irradiation with a carrier gas containing an inert gas, O_2 and H_2O to separate and purify astatine-211, and dissolving the astatine-211 in a solution (hereinafter to be referred to as step 2).

(step 1)

[0011] The α beam is irradiated to the metallic bismuth target by using an accelerator. As the accelerator, any accelerator capable of accelerating α beam to 30 MeV can be used. A high energy α beam ($^4He^{2+}$, 28.2 MeV) obtained in the accelerator is irradiated to a metallic bismuth target, and astatine-211 is produced in the bismuth target by the nuclear reaction ^{209}Bi (^4He, 2n) ^{211}At.

(Step 2)

[0012] A schematic drawing of one embodiment of an apparatus for carrying out step 2 is shown in Fig. 1. In the following, step 2 is explained by referring to Fig. 1.

[0013] A dry distillation method is applied to separate and purify astatine-211 from a metallic bismuth target irradiated with an α beam. Utilizing the high volatility of astatine-211, astatine-211 is separated and purified from the bismuth target by heating and melting the metallic bismuth target at a high temperature to selectively evaporate astatine-211 and collected by cooling. In the present invention, focusing on the fact that the volatility and reactivity of astatine vary depending on the chemical species of astatine, astatine oxide that is easily volatilized and dissolved is formed by devising the composition of the carrier gas (inert gas/O_2/H_2O mixed gas), and the distillation separation and dissolution recovery are performed easily and with high yield. The separation operation is performed, for example, by the following method.

[0014] The metallic bismuth target (astatine-211 is formed inside) irradiated with an α beam in step 1 is placed in a quartz tube in a tubular furnace. The temperature of the tubular furnace is increased to volatilize astatine-211 from the bismuth target. The volatilized astatine-211 is transported outside the quartz tube by a carrier gas (inert gas/O_2/H_2O mixed gas). The carrier gas oxidizes bismuth and astatine-211 to form the desired astatine oxide. The transported astatine-211 then passes through a Teflon connector, valve and tube. The Teflon tube is cooled outside the tubular furnace with ice water, liquid nitrogen etc. to adsorb astatine-211 to the tube wall. After all of the astatine-211 has volatilized from the bismuth (the radioactivity of astatine-211 in the cooled Teflon tube is saturated), a given amount of a solution (distilled water, alcohol such as methanol, saline, etc.) is passed through by a syringe pump to dissolve astatine-211 in the solution (distilled water, alcohol such as methanol, saline, etc.). Thereafter, the solution in which astatine-211 is dissolved (distilled water, alcohol such as methanol, saline, etc.) is extruded to obtain the desired astatine solution (aqueous solution, alcohol solution such as methanol solution, saline solution, etc.).

[0015] Examples of the inert gas include He, Ne, Ar, Kr, Xe, N_2 and the like, preferably, He or N_2.

[0016] The volume ratio of the inert gas:O_2 in the carrier gas is preferably 99:1 to 51:49, more preferably 90:10 to 60:40, further preferably 80:20 to 70:30. When the volume ratio of the inert gas:O_2 in the carrier gas is outside the above-mentioned range, astatine oxide is not formed and problems such as a decrease in the yield of astatine-211 and the like occur.

[0017] The content of H_2O in the carrier gas is preferably 1 to 15 $\mu g/cm^3$, more preferably 2 to 10 $\mu g/cm^3$, further preferably 5 to 8 $\mu g/cm^3$. When the content of H_2O in the carrier gas is outside the above-mentioned range, problems such as a decrease in the yield of astatine-211 and the like occur.

[0018] In a preferable embodiment of the present invention, the volume ratio of the inert gas:O_2 in the carrier gas is

99:1 to 51:49, and the content of H_2O is 1 to 15 $\mu g/cm^3$. In a more preferable embodiment of the present invention, the volume ratio of the inert gas:O_2 in the carrier gas is 90:10 to 60:40, and the content of H_2O is 2 to 10 $\mu g/cm^3$. In a further preferable embodiment of the present invention, the volume ratio of the inert gas:O_2 in the carrier gas is 80:20 to 70:30, and the content of H_2O is 5 to 8 $\mu g/cm^3$

[0019] The flow rate of the carrier gas is preferably 5 to 40 mL/min, more preferably 10 to 30 mL/min, further preferably 15 to 25 mL/min. When the flow rate of the carrier gas is outside the above-mentioned range, problems such as a decrease in the yield of astatine-211 and the like occur.

[0020] The temperature of the tubular furnace (that is, distillation temperature) is preferably 500 to 850°C, more preferably 650 to 850°C, further preferably 800 to 850°C. When the temperature of the tubular furnace is outside the above-mentioned range, problems such as a decrease in the yield of astatine-211 and the like occur.

[0021] Using the above-mentioned method, astatine-211 can be obtained as an aqueous solution that is easy to use for the synthesis of labeled drugs in a high yield and a high concentration, which strikingly expands the possibility of drug synthesis. In addition, by using a solvent other than water (e.g., alcohol such as methanol or saline) when trapping astatine-211, astatine-211 can be obtained as a solution other than an aqueous solution, which expands the range of medical and chemical utilization. Furthermore, the mechanism of the apparatus for carrying out step 2 of the method of the present invention is simple, and the development of an apparatus capable of automatically purifying astatine-211 for medical use can also be expected based on the present invention.

[Example]

[0022] The present invention is further explained in detail by the following Examples, which do not limit the present invention and may be varied without deviating from the scope of the present invention.

(Examples 1 - 6 and Comparative Examples 1 - 2)

(Step 1: Production of astatine-211)

[0023] A high energy α beam ($^4He^{2+}$, 28.2 MeV) obtained in the accelerator was irradiated to bismuth, and astatine-211 was produced in the bismuth by the nuclear reaction ^{209}Bi (^4He, 2n) ^{211}At.

Preparation of bismuth (Bi) target

[0024] Bi target was prepared by a vacuum vapor deposition method. A commercially available Bi metal (granular) was placed on a tantalum metal boat and set inside a vapor deposition apparatus. An aluminum (Al) foil (thickness 10 μm) was attached to the top of the metal boat as a backing for the target. After depressurizing the inside of the bell jar, the metal boat was heated with an electric current to volatilize the Bi metal and vapor deposit same on the Al foil. The vapor deposited Bi metal was obtained with a thickness of 5 to 30 mg/cm^2.

Irradiation to Bi target

[0025] The prepared Bi target was attached to the holder and the surface was covered with an aluminum foil (thickness 10 μm) to prevent scattering. Then, the entire holder was set at the irradiation position in the irradiation vessel. The Bi target was placed at an angle of 45 degrees to the beam axis direction to increase the cooling efficiency by widening as much as possible the area of the Bi target to be hit by the beam. The inside of the irradiation vessel was substituted with helium gas, and irradiated with an α beam of 1 to 2 μA. A 30 MeV α beam from the AVF cyclotron passed through the vacuum window (Havar foil) and aluminum cover and was injected to the Bi target at 28.2 MeV. During irradiation, helium gas was sprayed onto the Bi target at a flow rate of not less than 10 L/min to cool the target, and distilled water was flown into the target holder behind the beam to cool the target with water.

(Step 2: Separation and purification of astatine-211)

[0026] The Bi target after irradiation of the α beam was placed in a quartz tube, and set in a tubular furnace such that the Bi target was at the center of the tube. The downstream side was connected to a quartz tube and a Teflon trap for cooling (inner diameter 2 mm, length 20 cm) using a Teflon connector, a switching valve and a tube, and the upstream side was connected to a tube for introducing a mixed gas. After the connection, the valve at the top of the trap was closed to reduce the pressure in the quartz tube, and He/O_2/H_2O mixed gas (carrier gas) was introduced until the pressure in the system reached 1 atm. After reaching 1 atm, the valve was opened to flow the mixed gas to the cooling trap, trap, and exhaustion system. To prevent the deposition of volatile astatine oxide, the area from the tubular furnace outlet to

the top of the trap was heated to 130°C with a ribbon heater. The cooling trap was cooled with ice water while flowing the mixed gas, and the tubular furnace was heated to 850°C. In addition, a CdZnTe semiconductor detector was placed above the cooling trap to monitor the radiation (X-rays) emitted from astatine-211, and the heating was performed while confirming the collection in the cooling trap. Heating was continued for another 30 min after the tubular furnace temperature reached 850°C. Two valves at the top of the cooling trap were then operated to switch the pathway and the cooling trap was removed from the ice water. Using a syringe pump, 100 μL of distilled water was introduced into the cooling trap, air was sent using another syringe pump, and the 100 μL of distilled water was flown into the cooling trap at a flow rate of 250 μL/min to dissolve the collected astatine-211. Finally, an aqueous solution in which astatine-211 was dissolved was collected in a compact container.

[0027] The radiation of astatine-211 in the Bi target before distillation and the radiation of astatine-211 in the final compact container were measured with a germanium semiconductor detector to quantify the astatine-211 contained in each. The chemical yield under each condition was calculated with corrections for radioactive decay. The composition ($He:O_2$ volume ratio and H_2O content in the carrier gas) of the carrier gas and chemical yield were as follows.

[Table 1]

	$He:O_2$ volume ratio	H_2O content ($\mu g/cm^3$)	chemical yield (%)
Example 1	75:25	6.0	78
Example 2	75:25	5.5	74
Example 3	75:25	4.0	67
Example 4	75:25	2.5	64
Example 5	75:25	2.3	68
Example 6	75:25	1.4	52
Comparative Example 1	100:0	3.0	33
Comparative Example 2	100:0	3.1	37

(Examples 7 and 8)

[0028] In the same manner as in Examples 1 to 6 except that $N_2/O_2/H_2O$ mixed gas was used as the carrier gas, astatine-211 was obtained. The composition ($N_2:O_2$ volume ratio and H_2O content in the carrier gas) of the carrier gas and chemical yield were as follows.

[Table 2]

	$N_2:O_2$ volume ratio	H_2O content ($\mu g/cm^3$)	chemical yield (%)
Example 7	75:25	6.0	66
Example 8	75:25	3.5	63

[0029] As is clear from Tables 1 and 2, in Examples 1 - 8 in which an inert gas/O_2/H_2O mixed gas was used as the carrier gas (in particular, He or N_2 was used as the inert gas and the composition of the carrier gas (inert gas:O_2 volume ratio and H_2O content in the carrier gas) was set to a specific range), astatine-211 could be separated and purified in high yields.

[Industrial Applicability]

[0030] According to the present invention, a method capable of separating and purifying astatine-211 in a high yield and dissolving same in a solution is provided.

[0031] This application is based on patent application No. 2017-235141 filed in Japan, the contents of which are encompassed in full herein.

Claims

1. A method for producing astatine-211, comprising
a step of irradiating α ray to bismuth to produce astatine-211 in the bismuth, and
a step of distilling the bismuth that received α ray irradiation with a carrier gas comprising an inert gas, O_2 and H_2O to separate and purify astatine-211, and dissolving the astatine-211 in a solution.

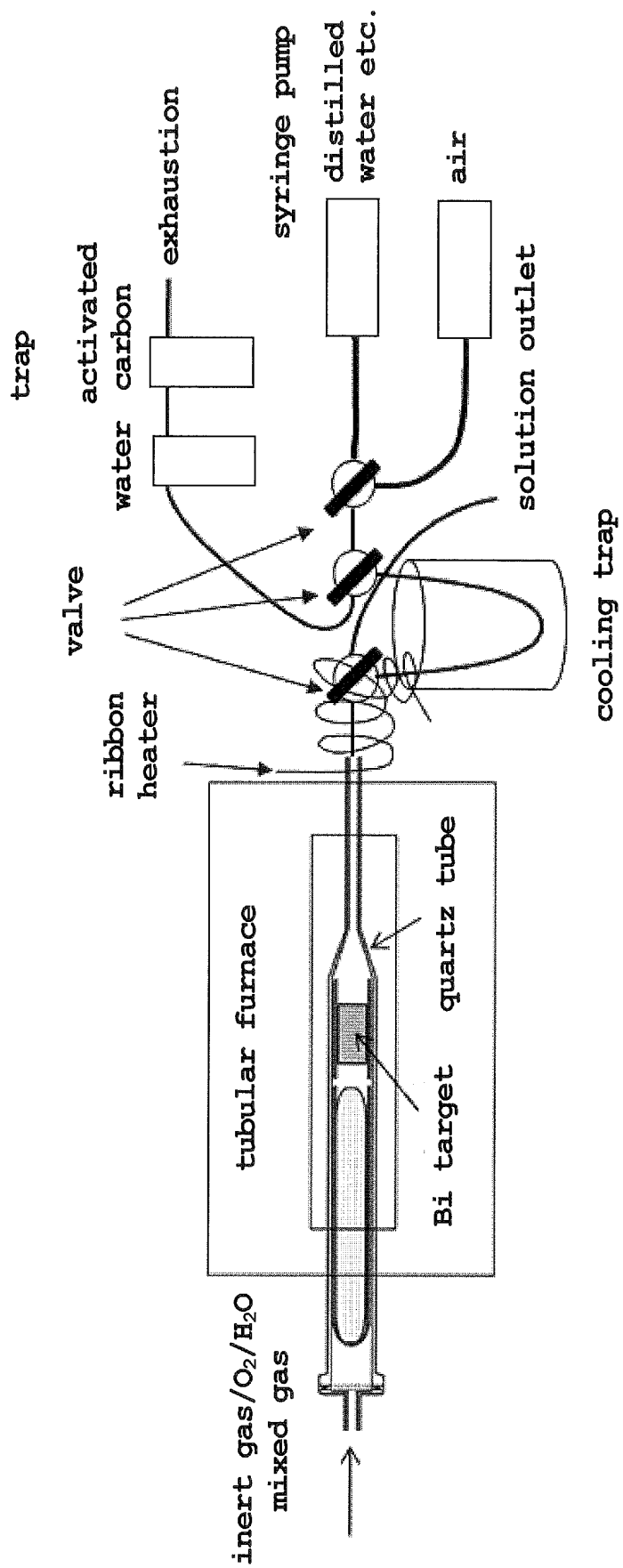
2. The method according to claim 1, wherein the inert gas is He or N_2.

3. The method according to claim 1 or 2, wherein the volume ratio of the inert gas:O_2 in the carrier gas is 99:1 to 51:49 and the content of H_2O is 1 to 15 $\mu g/cm^3$

4. The method according to any one of claims 1 to 3, wherein the flow rate of the carrier gas is 5 to 40 mL/min.

5. The method according to any one of claims 1 to 4, wherein the distillation temperature is 500 to 850°C.

Fig. 1


inert gas/O_2/H_2O mixed gas
tubular furnace
Bi target
quartz tube
ribbon heater
valve
trap
activated water carbon
exhaustion
syringe pump
distilled water etc.
air
solution outlet
cooling trap

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2018/045068

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl. C01B7/00(2006.01)i, G21G4/08(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl. C01B7/00, G21G1/00-7/00, G21H1/00-7/00, G21J1/00-5/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Published examined utility model applications of Japan	1922-1996
Published unexamined utility model applications of Japan	1971-2019
Registered utility model specifications of Japan	1996-2019
Published registered utility model applications of Japan	1994-2019

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
JSTPlus (JDreamIII), JST7580 (JDreamIII), JSTChina (JDreamIII)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	池田卓海 et al., 乾式分離法で得た211Atの薄層クロマトグラフィー並びに溶媒抽出挙動, 2017年日本放射化学年会・第61回放射化学討論会研究発表要旨集, 01 September 2017, vol. 2017-61st, p. 84, non-official translation (IKEDA, Takumi et al., "EXTRACTION AND THIN-LAYER CHROMATOGRAPHY BEHAVIOR OF 211At OBTAINED BY DRY DISTILLATION", Research presentation abstracts of the annual conference of the 2017 Japan Society of Nuclear and Radiochemical Sciences and the forum of the 61st Japan Society of Nuclear and Radiochemical Sciences)	1-5
A	豊嶋厚史 et al., アスタチンの酸化還元と溶媒抽出挙動, 2016日本放射化学会年会・第60回放射化学討論会研究発表要旨集, 01 September 2016, vol. 2016-60th, p. 112, non-official translation (TOYOSHIMA, Atsushi et al., "Redox and solvent extraction behavior of astatine", Research presentation abstracts of the annual conference of the 2016 Japan Society of Nuclear and Radiochemical Sciences and the forum of the 60th Japan Society of Nuclear and Radiochemical Sciences)	1-5

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 January 2019 (07.01.2019)	15 January 2019 (15.01.2019)

Name and mailing address of the ISA/	Authorized officer
Japan Patent Office 3-4-3, Kasumigaseki, Chiyoda-ku, Tokyo 100-8915, Japan	Telephone No.

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2018/045068

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	佐藤望 et al., 理研における At-211 製造, 第 53 回アイソトープ・放射線研究発表会要旨集, 2016, 53rd, p. 29, non-official translation (SATO, Nozomu et al., "At-211 is manufactured in RIKEN", Abstracts of the 53rd annual meeting on radioisotope and radiation research)	1-5
A	佐藤望 et al., 理研における At-211 製造, 2016 日本放射化学会年会・第 60 回放射化学討論会研究発表要旨集, 01 September 2016, vol. 2016-60th, p. 50, non-official translation (SATO, Nozomu et al., "At-211 is manufactured in RIKEN", Research presentation abstracts of the annual conference of the 2016 Japan Society of Nuclear and Radiochemical Sciences and the forum of the 60th Japan Society of Nuclear and Radiochemical Sciences)	1-5

Form PCT/ISA/210 (continuation of second sheet) (January 2015)

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- JP 2017235141 A **[0031]**

Non-patent literature cited in the description

- **E. ANEHEIM et al.** *Scientific Reports,* 2015, vol. 5, 12025 **[0003]**
- **K. NAGATSU et al.** *Applied Radiation and Isotopes,* 2014, vol. 94, 363-371 **[0003]**